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(54) Title: CYANOACRYLATE POLYMER COMPOSITIONS COMPRISING AN ANTIMICROBIAL AGENT

(57) Abstract

Disclosed are cyanoacrylate polymer compositions comprising a biocompatible solvent and a compatible antimicrobial agent. These compositions provide for formation of an antimicrobial polymeric cyanoacrylate film on mammalian skin.

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CYANOACRYLATE POLYMER COMPOSITIONS COMPRISING AN ANTIMICROBIAL AGENT

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to cyanoacrylate compositions comprising a cyanoacrylate polymer, a biocompatible solvent and an antimicrobial agent. These compositions provide for formation of antimicrobial cyanoacrylate polymer films on mammalian skin which films are useful as wound dressings, wound bandages, surgical incise drapes, and the like.

References

The following publications, patent applications and patents are cited in this application as superscript numbers:

[1] Hawkins, et al., U.S. Patent No. 3,591,676, for *Surgical Adhesive Compositions*, issued July 6, 1971

[2] Halpern, et al., U.S. Patent No. 3,667,472, for *Adhesive for Living Tissue*, issued June 6, 1972

[3] McIntire, et al., U.S. Patent No. 3,654,239, for *Process for the Preparation of Poly(α-Cyanoacrylates)*, issued April 4, 1972

[4] Barley, et al., International Patent Application Publication No. WO 93/25196, for *Methods for Treating Non-Suturable Wounds by Use of Cyanoacrylate Adhesives*, published December 23, 1993

[5] Barley, et al., *Methods for Treating Suturable Wounds by Use of Sutures and Cyanoacrylate Adhesives*, U.S. Patent No. 5,254,132, issued October 19, 1993

[6] Barley, et al., U.S. Patent Application Serial No. 08/200,953, for *Methods for Reducing Skin Irritation From Artificial Devices by Use of Cyanoacrylate Adhesives*, filed February 24, 1994

[7] Rabinowitz, et al., U.S. Patent No. 3,527,224, for *Method of Surgically Bonding Tissue Together*, issued September 8, 1970

[8] Kronenthal, et al., U.S. Patent No. 3,995,641, for *Surgical Adhesives*, issued December 7, 1976

[9] Davydov, et al., U.S. Patent No. 4,035,334, for *Medical Adhesive*, issued July 12, 1977

[10] Waniczek, et al., U.S. Patent No. 4,650,826, for *Stabilized Cyanoacrylate Adhesives Containing Bis-Trialkylsilyl Esters of Sulfuric Acid*, issued March 17, 1987

[11] Askill, et al., U.S. Patent Application Serial No. 08/781,279, filed January 10, 1997, entitled *Methods for Draping Surgical Incision Sites*

[12] Greff, et al., U.S. Patent No. 5,480,935, for *Cyanoacrylate Adhesive Compositions,* issued January 2, 1996

[13] Hagen, et al., "*A Comparison of Two Skin Preps Used in Cardiac Surgical Procedures*", AORN Journal, 62(3):393-402 (1995)

[14] Ritter, et al., "*Retrospective Evaluation of an Iodophor-Incorporated Antimicrobial Plastic Adhesive Wound Drape*", Clinical Orthopedics and Related Research, pp. 307-308 (1988)

[15] Osuna, et al., "*Comparison of an Antimicrobial Adhesive Drape and Povidone-Iodine Preoperative Skin Preparation in Dogs*", Veterinary Surgery, 21(6):458-462 (1992)

[16] O'Sullivan, et al., U.S. Patent No. 4,038,345, for *High Viscosity Cyanoacrylate Adhesive Compositions, and Process for Their Preparation*, issued July 26, 1977

[17] Beller, et al., U.S. Patent No. 2,706,701, for *Process for the Preparation of Iodine-Polyvinylpyrrolidone by Dry Mixing*, issued April 19, 1955

[18] Hosmer, U.S. Patent No. 2,826,532, for *Process of Stabilizing Polyvinylpyrrolidone*, issued March 11, 1958

[19] Siggin, U.S. Patent No. 2,900,305, for *Preparation of Iodine Polyvinylpyrrolidone Adducts*, issued August 18, 1958

[20] Joyner, et al., U.S. Patent Nos. 2,784,127, for *Plasticized Monomeric Adhesive Compositions and Articles Prepared Therefrom*, issued March 5, 1957

[21] Columbus, et al., U.S. Patent No. 4,444,933, for *Adhesive Cyanoacrylate Compositions with Reduced Adhesion to Skin*, issued April 24, 1984

[22] Leung, et al., U.S. Patent No. 5,328,687, for *Biocompatible Monomer and Polymer Compositions*, issued July 12, 1994

[23] Byram, et al., U.S. Patent No. 5,554,365, for *Use of Cyanoacrylate Adhesive Compositions to Inhibit Acute Radiation-Induced Skin Damage*, issued September 10, 1996.

[24] Tighe, et al., U.S. Patent No. 5,580,565, for "*Use of Cyanoacrylate Adhesives For Providing A Protective Barrier Film For The Skin*", issued on December 3, 1996.

[25] "*Kits Containing Cyanoacrylate Compositions Comprising an Antimicrobial Agent*", U.S. Patent Application Serial No.08/962,868, filed concurrently herewith as Attorney Docket No. 026446-111

All of the above publications, patent applications and patents are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent application or patent was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

Prepolymer cyanoacrylate ester compositions have been disclosed for a variety of topical uses on mammalian skin including use as a replacement for sutures or staples in closing the dermal layer of an incision after surgery.[1,2,5] Other disclosed topical uses include use as a hemostat[3], use in covering small non-suturable wounds on skin surfaces[4], use in inhibiting surface skin irritation arising from friction between the skin surface and artificial devices such as tapes, prosthetic devices, casts, etc.[6] and use in inhibiting acute radiation-induced skin damage.[23] Still another topical use of prepolymer cyanoacrylate esters is its use in the *in situ* formation of a surgical incise drape.[11]

Notwithstanding the beneficial properties associated with such prepolymer cyanoacrylate compositions and their suitability for topical applications, these compositions do not possess a sufficiently broad spectrum of antimicrobial activity,

including activity against microbial spores and, accordingly, cannot guarantee reductions in microbial populations on mammalian skin surface either under or adjacent a polymeric cyanoacrylate film formed on the skin. Many of the uses of cyanoacrylate adhesives enumerated above would, however, significantly benefit by a broad spectrum of antimicrobial property in the polymer film. Accordingly, incorporation of broad antimicrobial properties into the cyanoacrylate polymeric film necessitates, of course, that an antimicrobially effective amount of an antimicrobial agent be incorporated into the cyanoacrylate composition and that sufficient amounts of this agent be released from the polymeric cyanoacrylate film that an antimicrobial effect is achieved.

A problem has arisen in the use of these prepolymer cyanoacrylate ester compositions. Particularly, when some antimicrobial agents are added to the composition, it has been found that premature polymerization or inhibited polymerization occurs. For instance, as disclosed in U.S. Serial No. 08/912,681, filed August 18, 1997, some antimicrobial agents were found not to be compatible with the polymerizable cyanoacrylate monomer compositions, e.g. tetracycline hydrochloride. First, some antimicrobial agents were not soluble or dispersible in the cyanoacrylate monomer composition at the concentrations necessary to effect antimicrobial properties. Second, some antimicrobial agents employed caused premature polymerization of the cyanoacrylate monomer composition. Third, some antimicrobial agents employed prevented *in situ* polymerization of the cyanoacrylate monomer composition when applied to the skin, i.e., the composition did not cure. For example, it was found that elemental iodine (I_2) was only partially soluble in the polymerizable cyanoacrylate composition and prevented polymerization. Finally, some antimicrobial agents were not compatible with the intended use of the polymeric film because they inhibited formation of a flexible, durable film. Other antimicrobials caused premature polymerization, e.g., tetracycline hydrochloride caused polymerization within 24 hours of addition.

Because of these disparate properties, many conventional antimicrobial agents were found to be unsuitable for use in polymerizable cyanoacrylate compositions. However, in view of the clear benefits associated with the incorporation of an

antimicrobial agent directly into the cyanoacrylate composition, there is an ongoing need to formulate a cyanoacrylate composition which overcomes the above-noted problems caused by a variety of antimicrobial agents. This invention overcomes the problems associated with *in situ* polymerization of the cyanoacrylate monomer compositions comprising an antimicrobial agent.

SUMMARY OF THE INVENTION

This invention is directed to compositions comprising a cyanoacrylate polymer, a biocompatible solvent and an antimicrobially effective amount of an antimicrobial agent. It has been found that the problems of premature polymerization and non-curing of the cyanoacrylate monomer composition in the presence of certain antimicrobial agents may be avoided by a composition comprising a cyanoacrylate polymer, a biocompatible solvent and an antimicrobial agent. These compositions provide for formation of an antimicrobial cyanoacrylate polymer film on mammalian skin.

In practice, a cyanoacrylate polymer is dissolved in a biocompatible solvent which includes a compatible antimicrobial agent. This composition is then applied to the skin and a flexible, durable polymer film is formed on the skin as the biocompatible solvent dissipates. The specific antimicrobial agent employed is compatible with both the cyanoacrylate polymer and the biocompatible solvent.

Accordingly, in one of its composition aspects, this invention is directed to an antimicrobial cyanoacrylate composition which comprises:

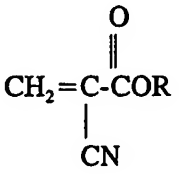
(a) a biocompatible solvent;

(b) a cyanoacrylate polymer; and

(c) an antimicrobially effective amount of an antimicrobial agent.

The biocompatible solvent is chosen such that it will dissipate from the composition once it has been applied to the skin. These include acetone, methyl ethyl ketone and esters such as ethyl acetate and mixtures thereof. Preferably, the solvent is acetone.

Preferably, the cyanoacrylate polymer is formed from a polymerizable monomer or reactive oligomer of a cyanoacrylate ester which, in monomeric form, is represented by formula I:



I

wherein R is selected from the group consisting of:

alkyl of 1 to 10 carbon atoms,

alkenyl of 2 to 10 carbon atoms,

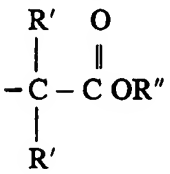
cycloalkyl groups of from 5 to 8 carbon atoms,

phenyl,

2-ethoxyethyl,

3-methoxybutyl,

and a substituent of the formula:



wherein each R′ is independently selected from the group consisting of:

hydrogen and methyl, and

R″ is selected from the group consisting of:

alkyl of from 1 to 6 carbon atoms,

alkenyl of from 2 to 6 carbon atoms,

alkynyl of from 2 to 6 carbon atoms,

cycloalkyl of from 3 to 8 carbon atoms,

aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl,

phenyl, and

phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

More preferably, in the cyanoacrylate esters of formula I, R is alkyl of from 2 to 10 carbon atoms and still more preferably alkyl of from 4 to 8 carbon atoms. Even more preferably, R is butyl, pentyl, octyl, decyl or mixtures thereof and most preferably, R is *n*-butyl.

The cyanoacrylate composition comprises a cyanoacrylate polymer in an amount from about 5 weight percent to about 60 weight percent of the composition, more preferably from 15 weight percent to about 45 weight percent of the composition.

The cyanoacrylate polymer is characterized as having a molecular weight from about 10,000 Daltons to about 500,000 Daltons and is selected to yield solutions of appropriate viscosity.

Antimicrobial agents would include antibacterials, anti-fungals, antibiotics, anti-virals and anti-parasitics. Specifically, these would include acyclovir, amphotericin B, bacitracin, butoconazole nitrate, carbol-fuchsin solution, chloramphenicol, chlortetracycline hydrochloride, ciclopirox olamine, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamycin sulfate, gentian violet, haloprogin, iodochlorhydroxyquin, ketoconazole, mafenide acetate, metronidazole, miconazole nitrate, mupirocin, naftifine, neomycin sulfate, nitrofurazone, nystatin, oxiconazole nitrate, silver sulfadiazine, sulconazole nitrate, tetracycline hydrochloride, tolnaftate, undecylenic acid and zinc undecylenate, benzyl benzoate, crotamiton, lindane, permethrin, pyrethrins, quaternary ammonium compounds, e.g., cetrimide, iodophors such as povidone-iodine, biguanide compounds such as chlorhexidine and its salts, e.g., chlorhexidine gluconate, and chlorophenols, e.g. MICROBAN® (Microban Products).

Preferred antimicrobial agents are povidone-iodine, chlorhexidine and its salts, e.g., chlorhexidine gluconate, neomycin sulfate, bacitracin, miconazole nitrate, naftifine, acyclovir and lindane.

The preferred antimicrobial agent is preferably employed at from about 0.5 to 40 weight percent based on the total weight of the polymer, more preferably at from about 1 to 20 weight percent based on the total weight of the polymer in the composition.

The antimicrobial cyanoacrylate polymer compositions preferably further comprise a biocompatible plasticizer to make the film flexible and durable. The preferred biocompatible plasticizer is dioctyl phthalate or C_2-C_4 acyl tri-n-alkyl (C_1-C_6) citrates which are preferably employed at from about 18 to 25 weight percent based on the total weight of the polymer absent the antimicrobial agent.

Another aspect of the invention is a kit of parts which comprises a cyanoacrylate polymer and a biocompatible solvent stored in a first container, and an antimicrobial agent stored in a second container. The kit may further comprise an applicator means on the first or second container.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is directed to cyanoacrylate compositions comprising an antimicrobially effective amount of a compatible antimicrobial agent. However, prior to discussing this invention in further detail, the following terms will first be defined.

Definitions

As used herein, the following terms have the following meanings:

The term "cyanoacrylate polymers" refers to polymerized cyanoacrylates which in their monomeric or oligomeric forms are preferably compounds represented by formula I as described above.

More preferably, in formula I, R is an alkyl group of from 2 to 10 carbon atoms including ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *n*-pentyl, *iso*-pentyl, *n*-hexyl, *iso*-hexyl, 2-ethylhexyl, *n*-heptyl, octyl, nonyl, and decyl. More preferably, R is butyl, pentyl, octyl, decyl and most preferably, R is *n*-butyl. Mixtures of such compounds can also be employed.

These polymerizable cyanoacrylate esters are known in the art and are described in, for example, U.S. Patent Nos. 3,527,224; 3,591,676; 3,667,472; 3,995,641; 4,035,334; and 4,650,826[1,2,7-10] the disclosures of each are incorporated herein by reference in their entirety.

The cyanoacrylate polymers described herein bond to human skin tissue without causing histotoxicity or cytotoxicity. A preferred cyanoacrylate polymer is poly (*n*-butyl-cyanoacrylate).

The cyanoacrylate composition comprises a cyanoacrylate polymer in an amount from about 5 weight percent to about 60 weight percent of the composition, more preferably from 15 weight percent to about 45 weight percent of the composition.

The cyanoacrylate polymer is characterized as having a molecular weight from about 10,000 Daltons to about 500,000 Daltons and is selected to yield solutions of appropriate viscosity.

The term "biocompatible solvent" refers to solvents which are compatible with mammalian skin as measured by the lack of moderate to severe skin irritation. Examples of biocompatible solvents include acetone, methyl ethyl ketone and esters such as ethyl acetate.

Solvents used in this invention are chosen such that once the composition is applied to the skin, the solvent quickly dissipates (less than 5 minutes) leaving a durable, flexible film. Accordingly, the solvent preferably is an organic solvent having a high vapor pressure.

The term "antimicrobial" or "antimicrobial agent" refers to agents which destroy microbes (i.e., bacteria, fungi, viruses, parasites, microbial spores and the like) thereby preventing their development and pathogenic action. These antimicrobial agents release from the cyanoacrylate polymer films once they have formed on the skin. Examples of these include: acyclovir, amphotericin B, bacitracin, butoconazole nitrate, carbol-fuchsin solution, chloramphenicol, chlortetracycline hydrochloride, ciclopirox olamine, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamycin sulfate, gentian violet, haloprogin, iodochlorhydroxyquin, ketoconazole, mafenide acetate, metronidazole, miconazole nitrate, mupirocin, naftifine, neomycin sulfate,

nitrofurazone, nystatin, oxiconazole nitrate, silver sulfadiazine, sulconazole nitrate, tetracycline hydrochloride, tolnaftate, undecylenic acid and zinc undecylenate, benzyl benzoate, crotamiton, lindane, permethrin, pyrethrins, quaternary ammonium compounds, e.g., cetrimide; iodophors such as povidone-iodine; biguanide compounds such as chlorhexidine and its salts; and chlorophenols, e.g. MICROBAN® (Microban Products).

Preferred antimicrobial agents are povidone-iodine, chlorhexidine and its salts, neomycin sulfate, bacitracin, miconazole nitrate, naftifine, acyclovir and lindane.

The term "biocompatible plasticizer" refers to any material which is soluble or dispersible in the cyanoacrylate composition, which increases the flexibility of the resulting polymer film coating on the skin surface, and which, in the amounts employed, is compatible with the skin as measured by the lack of skin irritation. Suitable plasticizers are well known in the art and include those disclosed in U.S. Patent Nos. 2,784,127[20] and 4,444,933[21] the disclosures of both of which are incorporated herein by reference in their entirety. Specific plasticizers include, by way of example only, acetyl tri-*n*-butyl citrate (~20 weight percent or less), acetyl trihexyl citrate (~20 weight percent or less) butyl benzyl phthalate, dibutyl phthalate, dioctylphthalate, *n*-butyryl tri-*n*-hexyl citrate, diethylene glycol dibenzoate (~20 weight percent or less) and the like. The particular biocompatible plasticizer employed is not critical and preferred plasticizers include dioctylphthalate or C_2-C_4 acyl tri-n-alkyl (C_1-C_6) citrates.

The term "solvent casting" refers to the technique wherein a preformed biocompatible cyanoacrylate polymer, dissolved in a biocompatible solvent is then applied to the skin and the solvent is allowed to dissipate thereby leaving a polymeric film on the skin. The compositions of this invention include an antimicrobial agent which is incorporated into the polymer layer as the solvent dissipates from the solution once it is applied to skin.

Compositions

This invention is based on the novel and unexpected discovery that by dissolving cyanoacrylate polymers in a biocompatible solvent, many antimicrobial agents may be incorporated into the composition to be applied to the skin. Accordingly, this solves the problem of premature polymerization and inhibition of polymerization caused by some antimicrobials previously seen in compositions where the cyanoacrylate esters were allowed to polymerize directly on the skin. Further, since polymerization has already occurred, the polymer film with an antimicrobial agent is formed by evaporation of the solvent once it has been applied to the skin. Moreover, the cyanoacrylate polymer composition comprising a biocompatible solvent and an antimicrobial agent forms a flexible, durable polymeric film having the antimicrobial incorporated therein which antimicrobial is released from the film in sufficient amounts to provide an antimicrobial property to the film when formed on mammalian skin.

Solvents which may be used in this invention are chosen such that they have a high vapor pressure and do not cause moderate to severe skin irritation. These include acetone, methyl ethyl ketone and esters such as ethyl acetate. Preferably acetone is used.

The compositions of this invention are prepared by adding polymerized cyanoacrylate to a biocompatible solvent and an antimicrobial agent. The polymerized cyanoacrylate is finely ground to a powder, preferably to less than 20 mesh size. The polymer powder is then added to the biocompatible solvent and stirred until dissolved. The antimicrobial agent is preferably added to the polymer/solvent mixture as a powder and is dispersed or dissolved in the cyanoacrylate composition. Mixing is employed to obtain a homogeneous solution or suspension. It is understood that the order of addition is not critical. The cyanoacrylate polymers may also be formed by controlled solution polymerization in the solvent prior to addition of the antimicrobial agent.

The amount of antimicrobial agent added to the cyanoacrylate composition is a sufficient amount such that the resulting polymeric film is antimicrobial. Preferably, from about 0.5 to about 40 weight percent of the antimicrobial is added and more

preferably from about 1 to 20 weight percent is added to the cyanoacrylate composition based on the total weight of the polymer in the composition.

The specific amount of antimicrobial required to effect antimicrobial properties in the resulting polymeric film can be readily measured by conventional *in vitro* assays measuring zones of microbial growth inhibition around the film. Zones of inhibition of at least 1 millimeter and preferably 3 millimeters from the edge of the film when tested in the manner of Example 3 below evidence that the polymeric film is antimicrobial. Assessing the amount of antimicrobial required in the cyanoacrylate polymer film to effect such a zone of inhibition is well within the skill of the art.

The composition of the biocompatible solvent, antimicrobial and the cyanoacrylate polymer can be formulated to a specific viscosity to meet disparate demands for the intended application of the composition. For example, relatively low viscosities are often preferred where application is to be made to a large surface area (e.g., abdominal surfaces). This preference results from the fact that these forms are less viscous and, accordingly, will permit more facile large surface area application of a thin application. Contrarily, where application is to be made to a specific position on the skin (e.g., elbow surfaces, knee surfaces and the like), higher viscosity materials are preferred to prevent "running" of the material to unintended locations.

Further, the preferred viscosity for the cyanoacrylate compositions of this invention will also be dependent upon the mode of application chosen. The clinician may choose the mode of application dependent on the size, shape and location of the skin to which the composition is to be applied. For example, application may be done by brush, swab, sponge, specially designed spatulas or applicators, syringe or spray. Spraying techniques may utilize inert gases, such as nitrogen, fluorocarbons or the like.

Accordingly, these compositions have a viscosity of from about 30 to 50,000 centipoise at 20°C. For low viscosity applications, viscosity ranges of from about 30 to 1,500 centipoise at 20°C are preferred. More preferably, the cyanoacrylate composition has a viscosity of from about 30 to about 500 centipoise at 20°C.

A thickening agent is optionally employed to increase the viscosity of the composition which thickening agent is any biocompatible material which increases the

viscosity of the composition. Suitable thickening agents include, by way of example, polymethyl methacrylate (PMMA) or other preformed polymers soluble or dispersible in the composition, a suspending agent such as fumed silica and the like, with PMMA being preferred. Fumed silica is particularly useful in producing a gel for topical application having a viscosity of from about 1500 to 50,000. Suitable thickening agents for the cyanoacrylate compositions described herein also include a polymer of the alkyl cyanoacrylate as disclosed in U.S. Patent Nos. 3,654,239[3] and 4,038,345[16] both of which are incorporated herein by reference in their entirety.

Thickening agents are deemed to be biocompatible if they are soluble or dispersible in the composition and are compatible with the skin as measured by the lack of moderate to severe skin irritation.

Alternatively, the viscosity of the composition may be adjusted by changing the polymer to solvent ratio, with greater concentrations of polymer yielding higher viscosity solutions, or adjusting the molecular weight of the cyanoacrylate polymer, with higher molecular weights yielding higher viscosity solutions, used in the composition.

The cyanoacrylate composition preferably includes a biocompatible plasticizer and such plasticizers are preferably included from about 10 to 30 weight percent and more preferably from about 18 to 25 weight percent based on the weight of the polymer in the composition absent the antimicrobial agent. A particularly preferred biocompatible plasticizer for use in the compositions described herein is dioctylphthalate or C_2-C_4 acyl tri-n-alkyl (C_1-C_6) citrates.

The cyanoacrylate compositions may additionally contain one or more optional additives such as colorants, perfumes, stabilizers, tackifiers, rubber modifiers, modifying agents, etc. In practice, each of these optional additives should be both miscible and compatible with the cyanoacrylate composition and the resulting polymer. Compatible additives are those that do not prevent the use of the cyanoacrylates in the manner described herein.

In general, colorants are added so that the polymer layer formed on the skin will contain a discrete and discernable color. Perfumes are added to provide a pleasant

smell to the formulation. Rubber modifiers are added to further enhance the flexibility of the resulting polymer layer. Tackifiers are added to improve the adhesion of the polymer film to the skin. The amount of each of these optional additives employed in the composition is an amount necessary to achieve the desired effect.

Additionally, the cyanoacrylate composition can optionally comprise a formaldehyde scavenger compound such as those described by Leung, et al.[22] The use of such scavengers has been suggested as enhancing internal *in vivo* applications of cyanoacrylates.

The cyanoacrylate composition may be provided sterile or may be sterilized as needed. The cyanoacrylate composition is stored at ambient conditions.

In an alternative embodiment, the cyanoacrylate composition is provided in a kit of parts which comprises the cyanoacrylate polymer and a biocompatible solvent stored in a first container and the antimicrobial agent in a second container. At the appropriate point in time the contents can be mixed together to form the composition described above. Preferably, the first and second container comprises an applicator means such that upon mixing of the components the composition can be applied to mammalian skin. Alternatively, separate applicator means can be employed in the kit. In a further preferred embodiment, the antimicrobial agent is chlorhexidine gluconate. The containers can be individual containers or a single container having a barrier separating the container into separate compartments. Alternatively, cyanoacrylate polymer is stored in a first container, the biocompatible solvent stored in a second container and the antimicrobial agent in a third container.

Kits similar to those described above are described in U.S. Patent Application No. 08/962,868,[25] filed concurrently herewith, as Attorney Docket No. 026446-111 and entitled "*Kits Containing Cyanoacrylate Compositions Comprising an Antimicrobial Agent.*" This application is herein incorporated by reference in its entirety.

Utility

The methods described herein are useful in forming a broad spectrum antimicrobial cyanoacrylate polymer film on the skin surface of a mammalian patient.

Such mammalian patients preferably include humans as well as domestic animals such as horses, cows, dogs, sheep, cats, etc.

The polymeric film finds particular utility in inhibiting microbial contamination thereunder and in the areas immediately adjacent thereto. Accordingly, such polymeric films can be used to topically cover small non-suturable wounds on skin surfaces which wounds do not penetrate through the dermal layer of the skin as in the manner described in Barley, et al.[4] When so employed, the antimicrobial cyanoacrylate composition is applied over the small non-suturable wound. Upon polymerization, an antimicrobial polymeric film is formed over the wound which provides for broad spectrum antimicrobial properties at the wound surface while also preventing exogenous contaminants from entering the wound.

Additionally, the polymeric films formed from the antimicrobial cyanoacrylate compositions described herein can also be used in the formation of a surgical incise drape in the manner described by Askill, et al.[11]. When so employed, the film strongly adheres to the mammalian skin surface to provide for a surgical incise drape which does not lift during surgery and has broad spectrum antimicrobial properties.

When used as either a small wound covering or as a surgical incise drape, the antimicrobial polymeric film will only adhere to the skin for a period of about 1-4 days after which time it sloughs off. This occurs because the cyanoacrylate polymer adheres only to the uppermost portion of the epidermal layer which is continuously in the process of being sloughed off and replaced by the underlying cells. Accordingly, the antimicrobial cyanoacrylate film need not be removed after application. However, if removal of the polymeric film is required, such can be accomplished with acetone (nail polish remover) or other biocompatible solvent.

Other utilities for the compositions of this invention include their use to form polymeric films in inhibiting surface skin irritation arising from friction between the skin surface and artificial devices such as tapes, prosthetic devices, casts, etc.[6], use in forming polymeric films in inhibiting acute radiation-induced skin damage[23], use in treating incontinence, dermatoses and areas adjacent to stomas.[24]

The following examples illustrates certain embodiments of the invention but are not meant to limit the scope of the claims in any way.

EXAMPLES

In the examples below, all temperatures are in degrees celsius (unless otherwise indicated) and all percents are weight percent (also unless otherwise indicated) except for percent inhibition which is true mathematical percentage. Additionally, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

CFU	=	colony forming units
conc.	=	concentration
flex.	=	flexibility
dur.	=	durability
ml	=	milliliters
mm	=	millimeters
ppm	=	parts per million
PVP-I_2	=	polyvinylpyrrolidone iodine complex
SAB-DEX	=	Sabouraud Dextrose
TSA	=	trypticase soy agar
gms	=	grams

COMPARATIVE EXAMPLE

The following example examines the compatibility of different antimicrobial agents in polymerizable cyanoacrylate monomer or oligomer compositions. This example shows the effect of several antimicrobial agents on polymerization of such compositions.

The composition employed monomeric *n*-butyl cyanoacrylate containing 100 ppm sulfur dioxide and 20 weight percent of dioctyl phthalate absent the antimicrobial agent. In each case, either 5 weight percent, 10 weight percent or 20 weight percent of the antimicrobial agent, based on the total weight of the composition, was added thereto and the properties of the resulting composition measured. The antimicrobial agents tested were elemental iodine, solid polyvinylpyrrolidone iodine, a 30% aqueous solution of polyvinylpyrrolidone iodine, silver nitrate, hexachlorophene, merbromin,

tetracycline·HCl, tetracycline hydrate, and erythromycin (each of these antimicrobial agents were obtained from commercial sources).

The evaluation included assessing whether the antimicrobial agent was soluble or suspendable in the composition; whether the resulting composition cured upon contact with skin; whether curing provided for a polymeric film *in situ* on the skin; whether the polymeric film was flexible and durable. Solubility and suspendability were determined by conventional standards. The ability of the resulting composition to cure *in situ* upon application to skin was measured by applying the cyanoacrylate composition onto the upper arm of a male human subject and determining whether polymerization proceeded (up to 5 minutes) and, if so, the time required for polymerization. Film forming capabilities on the skin were assessed by visual evaluation. Durability was assessed by determining whether the film was retained on the skin surface for at least 24 hours and flexibility was measured by the ability of the film to be retained on the skin without cracking or peeling for at least 24 hours. The results of this evaluation are summarized in Table I below:

TABLE I

Antimicrobial Agent	Conc.	Soluble	Curable	Film Formed	Flex.	Dur.
elemental iodine (I_2)	~20%	partially	No (when tested for 5 minutes)	--	--	--
PVP-I_2 solid	10%	no suspension[2]	Yes (30 seconds)	Yes	Yes	Yes
PVP-I_2 solution	10%	no, gelled[1]	--	--	--	--
Silver nitrate	5%	no, gelled[1]	--	--	--	--

Hexachloro-phene	5%	no, gelled[1]	--	--	--	--
Merbromin	5%	no, gelled[1]	--	--	--	--
tetracycline·HCl	5%	no, gelled[1]	--	--	--	--
tetracycline hydrate	5%	no, gelled[1]	--	--	--	--
Erythromycin	5%	no, gelled[1]	--	--	--	--

[1] gel formation within 24 hours of addition of the antimicrobial agent evidences premature polymerization of the cyanoacrylate. In such cases, the antimicrobial agent initiates polymerization.

[2] the mixture is readily resuspended with mild agitation. No gel formed over an 8 week period when stored at room temperature.

The above data demonstrates that of the antimicrobial agents tested, only polyvinylpyrrolidone iodine complex was compatible with the cyanoacrylate composition and, of the polyvinylpyrrolidone iodine complexes tested, only the solid form was compatible. The remaining antimicrobial agents were either insoluble in the solution and/or interfered with polymerization.

Examples 1 and 2 illustrate the preparation of compositions of this invention and the compatibility of antimicrobial agents therein.

EXAMPLE 1

Two grams of poly(n-butyl cyanoacrylate) and 8 grams of acetone were mixed at room temperature to form a solution and then 0.2 grams of PVP-I_2 were dispersed in the solution. Two drops of the composition were applied to the palm of an adult male and spread with the fingertip. The solvent rapidly dissipated forming a coherent polymeric film with the antimicrobial incorporated therein. The film was present four hours later.

EXAMPLE 2

Two grams of poly(n-butyl cyanoacrylate) and 8 grams of acetone were mixed at room temperature to form a solution and then either 0.2 gms of chlorhexidine diacetate or 0.05 gms tetracycline hydrochloride were dispersed in the solution. Two drops of each of the compositions were applied to the palm of an adult male and spread with the fingertip. The solvent rapidly dissipated forming a coherent polymeric film with the antimicrobial incorporated therein. The film was present four hours later.

EXAMPLE 3

The following example illustrates how the antimicrobial effects of a polymeric film of this invention can be determined.

A. Preparation of the Inoculum

Specifically, the surfaces of two TSA plates, 100 x 15 mm, are inoculated with stock cultures (maintained on TSA slants) with the following microorganisms using a sterile inoculating loop: *Staphylococcus aureus* (ATCC No. 6538) and *Staphylococcus epidermidis* (ATCC No. 12228). The plates are incubated at 30° to 35°C for 24 hours. The surfaces of two SAB-DEX agar plates are streaked with *Candida albicans* and incubated at 20-25°C for 48 hours.

The cultures are harvested with sterile saline. Each culture suspension is collected in a sterile container and sufficient sterile saline is added to reduce the microbial count to obtain a working suspension of approximately 1 x 10^8 CFU's per ml.

The specific microorganisms recited above are selected for inclusion herein because they are common human skin pathogens (bacteria and fungus).

B. Inoculation of Plates

Each of the three test microorganisms is used to inoculate individual TSA plates by streaking them with sterile cotton tip applicators saturated with the appropriate suspension. The plates are allowed to dry.

C. Inhibition Study

Films of the cyanoacrylate polymer compositions described in Example 2 comprising either chlorhexidine diacetate or tetracycline hydrochloride are formed on filter disks by applying the polymer/solvent/antibacterial to the filter and allowing the solvent to evaporate. The disks are then cut into approximately 11 to 13 mm^2 pieces. The pieces are placed in the center of the appropriate inoculated TSA plates (excluding tetracycline hydrochloride with *Candida albicans*). An untreated filter disk is cut into two pieces. One half is placed in the center of the appropriate inoculated TSA plate and the other half is placed in the center of uninoculated TSA plates, to serve as a negative control. Two inoculated plates of each microorganism are also used as positive controls without the test film filter disk. These plates are then incubated for 3 days at 30° to 35°C. After incubation, the plates are removed and examined for any signs of microbial growth inhibition.

Zones of inhibition extending at least 1 millimeter from the films evidence that the antimicrobial is leaching from the film and imparting antimicrobial properties to the film.

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

Claims:

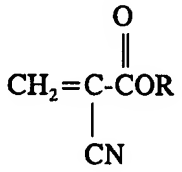
1. An antimicrobial cyanoacrylate composition which comprises:

(a) a biocompatible solvent;

(b) a cyanoacrylate polymer; and

(c) an antimicrobially effective amount of an antimicrobial agent.

2. The antimicrobial cyanoacrylate composition according to Claim 1 wherein the cyanoacrylate polymer is formed from a polymerizable monomer, reactive oligomer or mixtures of these of a cyanoacrylate ester which, in monomeric form, is represented by formula I:



I

wherein R is selected from the group consisting of:

alkyl of 1 to 10 carbon atoms,

alkenyl of 2 to 10 carbon atoms,

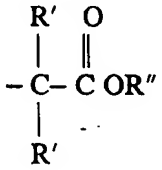
cycloalkyl groups of from 5 to 8 carbon atoms,

phenyl,

2-ethoxyethyl,

3-methoxybutyl,

and a substituent of the formula:



wherein each R′ is independently selected from the group consisting of:

hydrogen and methyl, and

R″ is selected from the group consisting of:

alkyl of from 1 to 6 carbon atoms,

alkenyl of from 2 to 6 carbon atoms,

alkynyl of from 2 to 6 carbon atoms,

cycloalkyl of from 3 to 8 carbon atoms,

aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl,

phenyl, and

phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

3. The antimicrobial cyanoacrylate composition according to Claim 2 wherein R is alkyl of from 4 to 10 carbon atoms.

4. The antimicrobial cyanoacrylate composition according to Claim 3 wherein R is alkyl of from 2 to 8 carbon atoms.

5. The antimicrobial cyanoacrylate composition according to Claim 4 wherein R is selected from the group consisting of butyl, pentyl, octyl, decyl or mixtures thereof.

6. The antimicrobial cyanoacrylate composition according to Claim 5 wherein R is *n*-butyl.

7. The antimicrobial cyanoacrylate composition according to Claim 2 wherein the amount of cyanoacrylate polymer is from about 5 weight percent to about 60 weight percent of the antimicrobial cyanoacrylate composition.

8. The antimicrobial cyanoacrylate composition according to Claim 1 wherein said antimicrobial agent is selected from the group consisting of chlorhexidine and its salts, miconazole and chlorhexidine gluconate.

9. The antimicrobial cyanoacrylate composition according to Claim 7 wherein the antimicrobial agent is chlorhexidine gluconate.

10. The antimicrobial cyanoacrylate composition according to Claim 1 wherein the amount of antimicrobial agent is about 0.5 weight percent to about 40 weight percent based on the weight of the polymer.

11. The antimicrobial cyanoacrylate composition according to Claim 1 wherein said biocompatible solvent is selected from the group consisting of acetone, methyl ethyl ketone and ethyl acetate.

12. The antimicrobial cyanoacrylate composition according to Claim 11 wherein said biocompatible solvent is acetone.

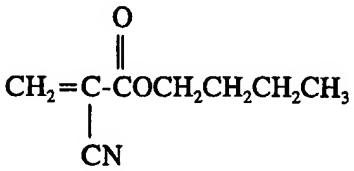
13. The antimicrobial cyanoacrylate composition according to Claim 1 which further comprises a biocompatible plasticizer.

14. The antimicrobial cyanoacrylate composition according to Claim 13 wherein said biocompatible plasticizer is dioctyl phthalate or C_2-C_4 acyl tri-n-alkyl (C_1-C_6) citrates.

15. An antimicrobial cyanoacrylate composition which comprises:

(a) acetone

(b) a cyanoacrylate polymer, which, in monomeric form, is represented by formula II:



II

(c) an antimicrobially effective amount of an antimicrobial agent.

16. A kit of parts which comprises a cyanoacrylate polymer and biocompatible solvent stored in a first container and a antimicrobial agent stored in a second container.

17. The kit of Claim 16 further comprising an applicator means on the first or second container.

18. The kit of Claim 16 in which the antimicrobial agent is chlorhexidine gluconate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/23423

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C08K 5/03, 5/17, 5/29
US CL : 523/122
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 523/122

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS
search terms: cyanoacrylate#, chlorhexidine, miconazole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,919,939 A (BAKER) 24 April 1990, col. 11, lines 1-19 and col. 11, line 54 to col. 12, line 42	1-10, 13 --- 1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 19 JANUARY 1999	Date of mailing of the international search report 29 JAN 1999
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